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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,725	10/01/2003	Michael G. Rosenblum	CLFR:029USD1	2944

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EXAMINER	
GODDARD, LAURA B	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 09/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/676,725	ROSENBLUM, MICHAEL G.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,7-10 and 13-29* is/are pending in the application.

4a) Of the above claim(s) *8,9,15,17-20 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,7,10,13,14,16,21, and 23-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/31/05, 7/6/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

8-30

DETAILED ACTION

1. The election filed August 8, 2005 in response to the restriction requirement of July 7, 2005 has been received. Applicant's election without traverse of Group II and species TNF-alpha as a biological response modifier is acknowledged.

2. Claims 5, 7-10, and 13-29 are pending. Claims 8, 9, 15, 17-20, and 22 are withdrawn. Claims 5, 7, 10, 13, 14, 16, 21, 23-39 are currently under prosecution.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 10, 21, and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The use of laboratory designations only to identify a particular antibody or antigen such as ZME-018 renders the claims indefinite because different laboratories may use the same laboratory designation to define completely distinct proteins or protein fragments. Amendment of the claims to include the deposit number for a hybridoma producing antibody ZME-018 or to unambiguously identify the antigen to which ZME-018 antibody binds, which would unambiguously define the claimed antibody and antigen, is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim is drawn to a monoclonal antibody that recognizes the ZME-018 antigen. Since a ZME-018 antibody is essential to the claimed invention it must be obtainable by a repeatable method set forth in the specification or otherwise readily available, the requirements of 35 USC 112 may not be satisfied by a deposit of the antibody or antigen to which it binds. The specification does not disclose a repeatable process to obtain the antibody and it is not apparent if the antibody is readily available to the public. It is noted that Applicant received antibody ZME-018 from Hybritech Inc as a gift (p. 28, Example 10), but there is no indication in the specification as to public availability. When the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific antibody will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required, would satisfy the deposit requirement made herein.

Amendment of the specification to recite the date of deposit and the complete

name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of the deposit.

5. Claims 21 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **written description** requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a protein with an antigen recognition site that recognizes and binds to the ZME-018 antigen. The specification does not provide sufficient distinguishing identifying characteristics of the genus of proteins that recognize and bind the ZME-018 antigen. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of a "ZME-018 antigen". There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus

Further, the following teaching of the court as set out in Noelle also clearly applies to the instant claimed invention. The court teaches as follows: "Noelle did not

provide sufficient support for the claims to the human CD40CR antibody in his '480 application because Noelle failed to disclose the structural elements of human CD40CR antibody or antigen in his earlier '799 application. Noelle argues that because antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described human CD40CR antibody by stating that it binds to human CD40CR antigen. Noelle cites Enzo Biochem II for this proposition. This argument fails, however, because Noelle did not sufficiently describe the human CD40CR antigen at the time of the filing of the '799 patent application. In fact, Noelle only described the mouse antigen when he claimed the mouse, human, and genus forms of CD40CR antibodies by citing to the ATCC number of the hybridoma secreting the mouse CD40CR antibody. If Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. Noelle did not describe human CD40CR antigen. Therefore, Noelle attempted to define an unknown by its binding affinity to another unknown. As a result, Noelle's claims to human forms of CD40CR antibody found in his '480 application cannot gain the benefit of the earlier filing date of his '799 patent application. Moreover, Noelle cannot claim the genus form of CD40CR antibody by simply describing mouse CD40CR antigen". *Randolph J. Noelle v Seth Lederman, Leonard Chess and Michael J. Yellin* (CAFC, 02-1187, 1/20/2004).

In the instant application, the specification only discloses ZME-018 antigen. The instant application does not however describe the ZME-018 antigen.

Since the instant application does not describe the genus of antigen to which the claimed proteins bind, the instant application cannot claim the genus form of protein by simply stating that they bind to the ZME-018 antigen. Thus the specification fails to describe the claimed protein that recognizes ZME-018 antigen, by the test set out in the example of Noelle. Since the specification fails to adequately describe the product to which the claimed method of treating cancer uses, it also fails to adequately describe the method.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 5, 7, 21, 24, 25, 28, and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent 4,590,071, as evidenced by Kirkwood et al (J of Clin Oncol, 1987 5:1247-1255, IDS).

The claims are drawn to a method of treating cancer in patients comprising administering a protein with an antigen recognition site directed toward a cell surface associated antigen conjugated or fused to a biological response modifier, wherein the patient's cancer expresses antigen recognized and bound by the protein (claim 5),

wherein the cancer is melanoma (claim 7), wherein the patient's cancer express an antigen recognized by a monoclonal antibody ZME-018 and wherein the protein is a monoclonal antibody that recognizes and binds the antigen (claim 10), wherein the protein is a monoclonal antibody (28, 29), wherein the protein binds the ZME-018 antigen (claim 21), wherein the protein is conjugated to the biological response modifier (claim 24), and wherein the protein recognizes and binds to the ZME-018 antigen (claim 25).

Kirkwood et al (J of Clin Oncol, 1987 5:1247-1255, IDS) discloses that the ZME-018 antibody binds to gp240, a 240kD melanoma-associated antigen that has exhibited greater restriction to melanoma than other antigens (p. 1247).

US Patent 4,590,071 teaches a method of treating melanoma in a human melanoma cell host by administering an amount of a conjugate of monoclonal antibody XMMME-001 or XMMME-002 with ricin toxin A chain (XMMME-001-RTA or XMMME-002-RTA) (col. 5, lines 27-60). The reference teaches that these monoclonal antibodies bind to the same melanoma associated antigen of approximately 240kD (col. 4, lines 25-26).

US Patent 4,590,071 does not teach that the 240kD antigen is gp240, however, the claimed antigen appears to be the same as the prior art antigen that ZME-018 antibody recognizes (Kirkwood et al). The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the

burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 5, and 26-29 rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 4,590,071, in further view of US Patent 4,753,894.

The claims are drawn to a method of treating cancer in patients comprising administering a protein with an antigen recognition site directed toward a cell surface associated antigen conjugated or fused to a biological response modifier, wherein the patient's cancer expresses antigen recognized and bound by the protein (claim 5), wherein the protein is an antibody (28), wherein the method of claim 5 further comprises identifying a patient having a tumor that comprises a cell surface antigen marker at concentrations in excess of that found at other non-target sites, obtaining a composition comprising a protein that recognizes the antigen conjugated or fused to a biological response modifier, and administering the composition to the patient (claim 26), wherein the patient is diagnosed as having a tumor with a specific antigenic

determinant that will allow concentration of the biological response modifier (claim 27), and wherein the protein is monoclonal antibody (claim 29).

US Patent 4,590,071 teaches as set forth above. The reference does not teach a method further comprising: identifying a patient having a tumor that comprises a cell surface antigen marker at concentrations in excess of that found at other non-target sites, obtaining a composition comprising a protein that recognizes the antigen conjugated or fused to a biological response modifier, wherein the patient is diagnosed as having a tumor with a specific antigenic determinant that will allow concentration of the biological response modifier and administering the composition to the patient, wherein the protein is a monoclonal antibody.

US Patent 4,753,894 teaches methods of diagnosing and treating cancer in patients by administering monoclonal antibodies that selectively bind said cancer (col. 3, lines 45-48; col. 4, lines 1-5, lines 38-41). The reference teaches the use of the monoclonal antibodies and labeled antibodies to diagnose or detect the presence of said cancer in a patient or to monitor it by immunoimaging or quantitative immunoassay procedures (col 5, lines 17-38).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add the detection/ diagnosis method steps taught by US Patent 4,753,894 to the method of treating cancer as taught by US Patent 4,590,071 because it is well-known in the art that the cancer tissue in a patient must be identified and specifically targeted for treatment so as not to disrupt the functions of healthy or normal tissues in the patient. US 4,753,894 teaches the additional steps of diagnosing a

patient with a tumor-associated antigen using monoclonal antibodies specific to the antigen and determining the amount of antigen expression in the patient or antigen target sites using imaging procedures, and administering a monoclonal antibody conjugated to a toxin that targets said antigen to treat the cancer. US 4,753,894 teaches the selective binding of the monoclonal antibody to cancer tissue which would allow targeting and concentration of the biological response modifier at the cancer expression site.

One would have been motivated to add the detection/ diagnosis method steps taught by US Patent 4,753,894 to the method of treating cancer as taught by US Patent 4,590,071 because identifying and locating a tumor-associated antigen in a patient and using monoclonal antibodies conjugated to a biological response modifier that selectively bind the antigen, would allow highly targeted treatment of the cancer tissue expressing the antigen, hence treating the patient's cancer.

8. Claims 5, 13, 14, and 16 rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 4,590,071, in further view of Blick et al (Cancer Research, 1987, 47:2986-2989).

The claims are drawn to a method of treating cancer in patients comprising administering a protein with an antigen recognition site directed toward a cell surface associated antigen conjugated or fused to a biological response modifier, wherein the

patient's cancer expresses antigen recognized and bound by the protein (claim 5), wherein the biological response modifier is a TNF-alpha cytokine (claims 13, 14, 16).

US Patent 4,590,071 teaches as set forth above. The reference does not teach the biological response modifier TNF-alpha.

Blick et al teach a method of treating cancer in a human patient with TNF-alpha with evidence of antitumor effects for some patients (p. 2988, col. 1; p. 2989, col. 1). It is well known in the art and the reference teaches that cytokines are known to have cytostatic and cytotoxic effects against a wide range of human tumor cells.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the TNF-alpha taught by Blick et al for the ricin toxin A (RTA) conjugated to the antibody because TNF-alpha is a well known biological response modifier that has antitumor activity and is a natural defense against tumors produced by activated macrophages. One would have been motivated to substitute the TNF-alpha for the RTA because of its known antitumor effects and for the advantages of conjugating TNF-alpha to an antibody to specifically target the antitumor effects.

9. Claims 5 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 4,590,071, in further view of Ghose et al (Crit Rev Ther Drug Carrier Syst, 1987, 3:263-359).

The claims are drawn to a method of treating cancer in patients comprising administering a protein with an antigen recognition site directed toward a cell surface

associated antigen conjugated or fused to a biological response modifier, wherein the patient's cancer expresses antigen recognized and bound by the protein (claim 5), wherein the protein with an antigen recognition site is fused to the biological response modifier (claim 23).

US Patent 4,590,071 teaches as set forth above. The reference does not teach the fusion of the protein and biological response modifier.

Ghose et al teach recombinant technology to create hybrid antibody molecules that are directed against the tumor-associated antigen and linked to biological products with antitumor activity such as tumor necrosis factor (p. 334).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to incorporate an antibody fused to a biological response modifier as taught by Ghose et al into the method of US Patent 4,590,071 because Ghose et al teach the advantage of a fused molecule as a "tailored antibody molecule" (p. 334) wherein genetic engineering can create one molecule to both target and treat a cancer cell. Ghose et al also teach the advantage of a fused molecule ove a conjugated molecule because fused molecules produced from transfection methods are more likely to be free of contaminating oncogenic viruses and nucleic acids as opposed to monoclonal antibodies produced by malignant cells used for conjugation to a biological response modifier (p. 334). One would have been motivated to incorporate an antibody fused to a biological response modifier into the method taught by US Patent 4,590,071 because Ghose et al teach the advantages of being able to tailor a fused molecule to comprise the desired target antibody and biological response modifier, and the

production of fused molecules resulting in less contamination, a factor important in the manufacture of drugs for treating cancer in human patients.

It would have been *prima facie* obvious and one would further have been motivated to make the construct of the combined references given the teaching in the specification that an "immunoconjugate may be a fusion protein prepared by genetic engineering methods known to those in the art" (p. 4).

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

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Art Unit 1642